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Can biochemical markers help in the differential diagnosis of pheochromacytoma-adrenocortical adenoma

The differential diagnosis of pheochromacytoma-adrenocortical adenoma

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Abstract

Aim: In this study, we aimed to investigate the usability of biochemical parameters in differentiating pheochromocytoma and nonfunctional adrenocortical adenomas.

Material and Methods: This study was conducted retrospectively by comparing 49 patients who underwent adrenalectomy and were pathologically diagnosed with 'pheochromocytoma' with 60 age- and sex-matched controls with nonfunctional adrenocortical adenomas between January 2000 and June 2022. Hematological markers such as neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), RDW, and MPV were compared between groups.

HALP score was calculated with the formula including hemoglobin (g/dl), albumin (g/L), lymphocyte (x103 /µl) and thrombocyte (x10^3 /µl) values [HALP score: Hemoglobin(g/dl)X albumin (g/L))X lymphocyte (x10^3 /µl)/ platelet (x10^3 /µl)]. HALP scores were compared between groups. At the same time, the effectuality of the HALP score in the differential diagnosis of pheochromocytoma was evaluated.

Results: While NLR and PLR values were statistically higher in pheochromocytoma patients compared to nonfunctional adenoma patients (p=0.009; p<0.001, respectively), HALP values were significantly low (p<0.001). There was no statistically significant difference in RDW and MPV values (p=0.072; p=0.509). When the diagnostic decision-making in predicting pheochromocytoma disease was examined by ROC curve analysis, it was found that the AUC values of the initial HALP, albumin, hemoglobin, and lymphocyte parameters were statistically significant.

Discussion: It was observed that biochemical parameters such as NLR, PLR, and HALP scores differed significantly in differentiating pheochromocytomas from nonfunctional ACAs. This difference was thought to be due to a severe inflammatory response in pheochromocytoma.

Keywords
Pheochromocytoma, Adrenocortical Adenomas, Halp Score

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Introduction

While the prevalence of adrenal tumors is 1-8.7% in autopsy series, it reaches 10%, especially in the elderly population, most of which are adrenocortical adenomas (ACA) when radiological examinations are evaluated [1]. While most ACAs are nonfunctional, 10-15% secrete hormones (Cushing's syndrome, Hyperaldosteronism) [2]. Otherwise, adrenocortical carcinomas seen in 1-2 per million and catecholamine-secreting pheochromocytomas originating from the adrenal medulla are also among the adrenal tumors [3]. In differential diagnosis, imaging methods are as important as clinical and laboratory evaluations. However, all evaluations may be insufficient to characterize the tumor. Therefore, alternative biochemical parameters have emerged for differentiating adenoma and non-adenoma masses.

Recently, hematological parameters such as neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), red cell distribution width (RDW), mean platelet volume (MPV) have been used as an indicator of acute and chronic inflammation in the prediction of inflammatory diseases and some malignancies [4, 5].

Apart from these parameters, a new index called HALP, which includes the immune system, a combination of hemoglobin, albumin, lymphocytes, and platelets, and the patient's nutritional status, has been found. This index [6, 7], which is used as a prognostic marker in various cancers, has recently started to take place in studies as a diagnostic marker to predict the disease [8] .

Our study aimed to demonstrate the role of biochemical markers in the differential diagnosis of nonfunctional ACAs and pheochromocytoma and whether the HALP score would affect predicting pheochromocytoma.

Material and Methods

This retrospective study was conducted between January 2000 and June 2022 at Karadeniz Technical University, Department of Endocrinology and Metabolic Diseases in Turkey. Preoperative polyclinic records of 49 patients who underwent adrenalectomy and were pathologically diagnosed with 'pheochromocytoma' were reviewed. The primary demographic characteristics (age, gender, etc.), chronic diseases as well as routine biochemical and radiological evaluations of the patients were recorded. Patients with ICD CODE D35.0-Adrenal gland benign neoplasm were scanned in the polyclinic records, and a control group was created with similar ages and gender.

Patients with active infection, inflammatory (ankylosing spondylitis, FMF, etc.), and a hematological disease affecting hemogram parameters were excluded from the study. Patients with any hormone-secreting adenoma based on the hormonal evaluation of the control group were excluded.

Systemic hematological inflammatory markers based on complete blood counts, such as neutrophil ratio (NR), lymphocyte ratio (LR), NLR, PLR, RDW, and MPV, were compared between groups. NLR was found via the division of the neutrophil count by the lymphocyte count, and PLR was found via the division of the platelet count by the lymphocyte count.

HALP score was calculated with the formula consisting of hemoglobin(g/dl), albumin (g/L), lymphocyte (x10^3 /µl) and thrombocyte (x10^3 /µl) values [HALP score: Hemoglobin (g/dl) X albumin (g/L)) X lymphocyte (x10^3 /µl) / platelet (x10^3 /µl)]. HALP scores were compared between groups. At the same time, the effectuality of the HALP score in the differential diagnosis of pheochromocytoma was evaluated.

Imaging methods determined the maximum tumor size and compared between groups.

SPSS 24.0 statistical package program was used in the data analysis. Descriptive statistics of results: number and percentage for categorical variables, mean, standard deviation, median, first quartile, and third quartile (Q1-Q3) for numerical variables. In comparisons of numerical variables between two independent groups, T-test was used in independent groups when the normal distribution condition was met, and the Mann-Whitney U test when it was not. In comparing numerical variables beween two dependent groups, the T-test was used in dependent groups when the normal distribution condition was met, and the Wilcoxon test was used when not. The Chi-square test was used to compare independent categorical variables. Diagnostic decision-making in predicting pheochromocytoma disease was examined by ROC curve analysis. The statistical alpha significance level was accepted as $p<0.05$

Ethical Approval

This study was approved by the Ethics Committee of the Faculty of Medicine, Karadeniz Technical University (Ethical approval date 2022-06-30, no:2022/125).

Results

Of the 109 patients included in the study, 49 (45.0%) were diagnosed with pheochromocytoma, and 60 (55.0%) with nonfunctional adenoma. There was no statistically significant difference between the groups regarding age and gender ($p>0.05$). Hypertension, diabetes mellitus, and coronary artery disease, among the comorbidities were statistically higher in patients with pheochromocytoma than in patients with nonfunctional adenoma ($p<0.05$). Tumor size was statistically more significant in pheochromocytoma patients than in nonfunctional adenoma patients ($p<0.001$). While MRI, MIBG,

Table 1. Comparison of Demographic Data, Comorbidities, and Tumor-Related Information Between Groups

		Pheochromocytoma (n=49) N(%)	Nonfunctional Adenoma (n=60) N(%)	p
Age ¹		47 (32,5-57)	47 (44,3-52)	0,604*
Gender ¥	Female	33 (67,3)	38 (63,3)	0,662**
	Male	16 (32,7)	22 (36,7)	
Hypertension		40 (81,6)	22 (36,7)	<0,001**
Diabetes Mellitus		16 (32,7)	9 (15,0)	0,029**
Coronary Artery Disease		5 (10,2)	0 (0,0)	0,016**
Tumor Size (mm) ¹		42 (33-56,5)	15,5 (12-20,8)	<0,001*
Tumor Area	Right	30 (61,2)	26 (43,3)	0,173**
	Left	18 (36,7)	31 (51,7)	
	Bilateral	1 (2,0)	3 (5,0)	
Imaging	MRI	35 (71,4)	29 (48,3)	0,015**
	CT	43 (87,8)	12 (75,0)	0,093**
	MIBG	13 (26,5)	0 (0,0)	<0,001**
	PET	11 (22,4)	0 (0,0)	<0,001**

¹Median (Q1-Q3), ¥ n (%), *Mann-Whitney U Test, **Chi-Square Test

and PET imaging were higher in pheochromocytoma patients (p<0.05), there was no significant difference between the groups in terms of CT imaging (p=0.093) (Table 1).

The comparison of laboratory values between the groups is demonstrated in Table 2. NLR and PLR values were statistically higher in pheochromocytoma patients compared to nonfunctional adenoma patients (p=0.009; p<0.001, respectively); HALP values were significantly low (p<0.001). There was no statistically significant difference in RDW and MPV values (p=0.072; p=0.509).

When the diagnostic decision-making in predicting pheochromocytoma disease was examined by ROC curve analysis, it was found that the AUC values of the initial HALP, albumin, hemoglobin, and lymphocyte parameters were statistically significant (Figure 1 and Table 3).

Table 2. Comparison of Laboratory Values Between Groups

	Pheochromocytoma (n=49)	Nonfunctional Adenoma (n=60)	p
NLR‡	2,52 (1,75-3,26)	1,94 (1,45-2,53)	0,009*
PLR‡	152,48 (123,41-192,78)	107,75 (88,25-155,70)	<0,001*
RDW‡	13,60 (12,95-14,70)	13,05 (12,60-14,08)	0,072*
MPV◦	14,0±1,5	13,7±1,9	0,509**
HALP‡	0,34 (0,26-0,40)	0,52 (0,39-0,68)	<0,001*

‡ Median (Q1-Q3), ◦ Mean±Standard Deviation, *Mann-Whitney U Test, **Independent Gropus T Test

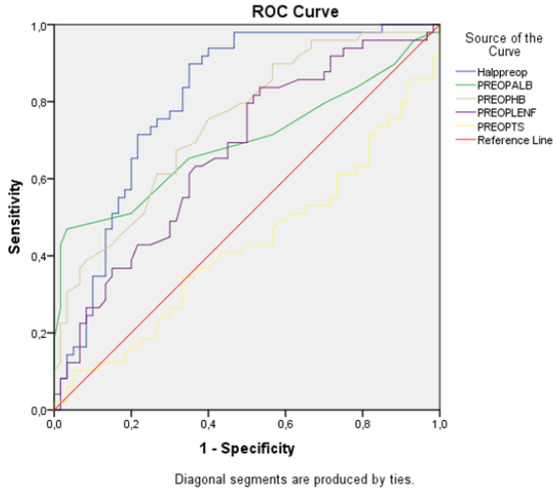

Figure 1. ROC analysis curve results of markers.

Table 3. Diagnostic usefulness of markers in predicting pheochromocytoma.

Variables	AUC	p	%95 CI
Halppreop	0,806	<0,001	0,723-0,889
PREOPALB	0,695	<0,001	0,589-0,801
PREOPHB	0,745	<0,001	0,653-0,836
PREOPLENF	0,668	0,003	0,566-0,769
PREOPTS	0,426	0,182	0,315-0,536

AUC: Area Under Curve

Discussion

In our study, NLR and PLR rates were statistically higher than ACAs, and the HALP score was significantly lower in pheochromocytoma patients. These results demonstrated that NLR, PLR, and HALP scores could be used to diagnose ACA and pheochromocytomas.

The classic triad of symptoms in patients with pheochromocytoma consists of episodic headache, sweating, and tachycardia. About half have paroxysmal hypertension; most have essential hypertension or normal blood pressure [9]. Abnormalities in carbohydrate metabolism (insulin resistance, impaired fasting glucose, significant type 2 diabetes mellitus) are directly related to increased catecholamine production. Therefore, an increased incidence of diabetes can be observed [10]. The frequency of diabetes and hypertension was higher than in those with nonfunctional adenoma, similar to the literature in our study.

There are limited studies in which biochemical parameters are evaluated in pheochromocytoma. In the study conducted by Arıkan et al. [11], in which 52 patients were evaluated, there was a significant difference between the two groups regarding PLR and RDW. While there was no difference in NLR and RDW in that study, in our study, no significant difference was found in RDW,however NLR rate statistically found to be important. Guadagno et al. reported that the local immune response in pheochromocytoma, a tumor originating from the adrenal medulla, is not different from other adrenal tumors, unlike our study [12]. Catecholamine excess secretion in pheochromocytoma triggers a systemic immune response and causes platelet increase more than lymphocyte increase. For this reason, PLR results were thought to be higher than ACA in pheochromocytoma in our study.

Studies demonstrate that while the neutrophil count increases in functional ACAs, the lymphocyte count decreases, increasing the NLR rate [13]. The fact that the ACA group was selected from nonfunctional adenomas in our study was one of the reasons for the significant difference between pheochromocytoma and ACA.

Recent studies have proven that the HALP score shows the nutritional and inflammation status of the patients and therefore is a good prognostic indicator [14, 15]. Lymphocytes and platelets are associated with the immune system, while hemoglobin and albumin provide information about the person's nutritional status. Anemia and thrombosis are exacerbated, while lymphocytes tend to decrease in inflammation. This scoring system was first evaluated in gastric cancer [16] and later used as a prognostic factor in many cancer types [7, 17]. Our study evaluated whether the immune response due to excessive catecholamine secretion in pheochromocytoma was associated with the HALP score and whether it differs from nonfunctional ACAs. In comparing the two groups, the HALP score was statistically significantly lower in the pheochromocytoma group. Our study is the first in the literature on this subject.

The HALP score, which has been used in many studies on survival in recent studies, has now been discussed in a few studies to predict disease. In the differential diagnosis of benign prostatic hyperplasia and prostate cancer, there was no difference in the ROC analysis regarding the area under the curve (AUC)

in the HALP score; however, the albumin evaluation was significant [8]. In our study, ROC analysis found the HALP score, albumin, hemoglobin, and lymphocyte count to be significant in differentiating pheochromocytoma from nonfunctional adenomas. These data were found to be important in terms of predictability and differential diagnosis of pheochromocytoma.

Limitation

This is a single-center and retrospective study. A limitation of the study is the limited number of patients due to the fact that pheochromocytoma is a rare disease and the lack of similar studies in the literature. In addition, among the limitations of the study, since the study period included the COVID-19 pandemic period, vaccination data that may affect hematologic parameters could not be accessed due to the retrospective study design.

Conclusion

In our study, NLR, PLR and HALP score were found to be important in differentiating pheochromocytomas from nonfunctional ACAs. It was considered that a severe inflammatory response in pheochromocytoma caused this difference. Since it is not always possible to distinguish pheochromocytomas by hormonal evaluation and radiological examination, these biochemical parameters will be helpful in the differential diagnosis. This study demonstrated that a simple blood count and biochemistry examination can give physicians an idea about the functionality of adrenal adenomas in the outpatient clinic. There are few studies on this subject, our study will contribute to the literature.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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